Remarks

Claims 1-13 and 21-30 were pending in the subject application. Claims 4-6, 12, and 28-30 remain pending but withdrawn from consideration. Accordingly, claims 1-13 and 21-30 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

Claims 1-3, 7-11, 13, and 21-27 have been rejected under 35 USC §112, first paragraph, as lacking sufficient written description. Applicants respectfully maintain that the subject specification provides a sufficient written description of the claimed invention. As acknowledged in the Office Action, possession of a claimed genus can be established by providing, in the specification, sufficient distinguishing identifying characteristics of the genus. In addition to the two inhibitors referenced at page 5 of the Office Action (RO318220 and PKC-α/β pseudosubstrate peptide), the specification discloses many more PKC inhibitors, and classes of PKC inhibitors, which are representative of the claimed genus. The subject specification describes a multitude of PKC inhibitory molecules, such as those listed in claim 4, *i.e.*, AG 490, PD98059, staurosporine, Ro-31-7549, Ro-31-8425, Ro-32-0432, sangivamycin; calphostin C, safingol, D-erythro-sphingosine, chelerythrine chloride, melittin; dequalinium chloride, Go6976, Go6983, Go7874, polymyxin B sulfate; cardiotoxin, ellagic acid, HBDDE, 1-O-Hexadecyl-2-O-methyl-rac-glycerol, hypercin, K-252, NGIC-J, phloretin, piceatannol, tamoxifen citrate, flavopiridol, and bryostatin 1. As Applicants noted in their response to the previous Office Action, different classes of PKC inhibitors and their preparation, and/or commercial sources of availability are described in U.S. Patent Nos. 5,621,101; 5,621,098; 5,616,577; 5,578,590; 5,545,636; 5,491,242; 5,488,167; 5,481,003; 5,461,146; 5,270,310; 5,216,014; 5,204,370; 5,141,957; 4,990,519; and 4,937,232, which are incorporated by reference at page 41 of the specification. Many other inhibitors of PKC were also known in the art at the application's filing date. An ordinarily skilled artisan, having the benefit of the teachings of the subject specification, would reasonably expect that any agent that inhibited PKC would also be effective in inhibiting RSV infection in an animal. Thus, Applicants respectfully assert that the subject specification does provide adequate written description for the genus of PKC inhibitors.

In addition to the chemical compounds listed above, Applicants again note that various oligonucleotide inhibitors of PKC are known in the art. U.S. Patent Application Publication 2003/0148989 (Bennet *et al.*), teaches oligonucleotide inhibition of PKC *in vivo* for treatment of cancer and other diseases. The Examples in the Bennet *et al.* publication indicate that reduction of PKC expression and inhibition of tumor growth were achieved *in vivo*. Examples of U.S. patents describing oligonucleotide inhibitors of PKC and inhibition of PKC expression *in vivo* include, but are not limited to, Nos. 6,537,973; 6,339,066; 6,190,869; 6,117,847; 6,015,892; 5,959,096; 5,916,807; 5,885,970; 5,882,927; and 5,703,054. Furthermore, RNA interference-mediated inhibition of PKC-alpha expression, including target sequences within the human PKC-alpha gene and corresponding interfering nucleic acid sequences, are described in U.S. Patent Application Publication No. WO 03/070983 A1 (see, for example, Tables I and II at pages 116-121), for the treatment of cancer and other diseases. Having the structure and sequence of the target gene (PKC), the teachings of the specification, and many examples of nucleic acid inhibitors of PKC in the art, Applicants submit that one skilled in the art would readily envision target nucleic acid sequences with the recipient mammal's mRNA and corresponding inhibitory nucleic acid molecules.

The Office Action indicates that the claims do not recite any specific structure of PKC inhibitor, such as a sequence of interfering RNA. As evidenced above, there is an abundance of chemical compounds and nucleic acid molecules known in the art which have established PKC inhibitory activity, several of which are specifically referred to in the specification. Applicants again assert that a specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known and already available to the public. *In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 221 USPQ 481, 489 (Fed. Cir. 1984). Thus, the subject specification need not teach those inhibitors of PKC which are well known in the art.

The nucleic acid PKC inhibitors recited in the claims are not described by function alone. Structural attributes of interfering RNA and antisense oligonucleotides, for example, including size and content, were known in the art at the time the application was filed. Furthermore, having the nucleotide sequence of the target gene provides discerning information regarding the sequences (*i.e.*,

structural information) of other suitable inhibiting nucleic acid molecules, and leads one of ordinary skill in the art to their selection. Accordingly, the teaching of the subject specification, knowledge of the sequence and structure of the PKC gene, and the nucleic acid PKC inhibitors that others have developed for treatment of other disease states provides sufficient structural and functional correlates to describe the genus of target PKC sequences and corresponding nucleic acid inhibitors. The Examiner appears to have acknowledged that the state of the art at the subject application's filing date was sufficiently developed such that the design and use of RNAi molecules to inhibit expression of a target gene *in vitro* is well established.

In view of the abundance of PKC inhibitors available at the time the subject application was filed, the subject application conveys to those skilled in the art that, as of the application's filing date, Applicants were in possession of the genus of PKC inhibitors and that those inhibitors would reasonably be expected to inhibit RSV infection in an animal, as recited in the claims. Thus, Applicants submit that the subject specification contains sufficient disclosure to convey to one of ordinary skill in the art that Applicants had possession of the claimed method. Accordingly, reconsideration and withdrawal of the rejection under 35 USC §112, first paragraph, is respectfully requested.

Claims 1-3, 7-11, 13, and 21-27 have been rejected under 35 USC §112, first paragraph, as non-enabled by the subject specification. The Office Action indicates that the subject specification does not provide sufficient guidance to teach one skilled in the art to use the nucleic acid inhibitors such as interfering RNA targeted to PKC mRNA *in vivo*. Applicants respectfully maintain that the claimed invention is fully enabled by the subject specification.

To the extent Applicants' remarks set forth above in response to the rejection under 35 USC §112, first paragraph, for lack of written description, are applicable to the non-enablement rejection, the remarks are incorporated herein by reference. Moreover, Applicants respectfully maintain that the data and teachings presented in the subject application establish that PKC inhibition can be used to inhibit RSV infection. The data in the application shows that PKC activity is required for proper location of RhoA at the cell membrane for successful RSV infection. The state of the art was sufficiently developed such that tools and methods for achieving the required PKC inhibition were appreciated by the inventors, taught in the patent application, and available to those of ordinary skill

in the art. Thus, Applicants submit that the patent application contains sufficient disclosure to enable one of ordinary skill in the art to carry out the methods of the invention without undue experimentation.

The Examiner asserts under this rejection that "applicant submitted only counsel's arguments without supporting evidence..." Applicants respectfully assert that the arguments submitted were supported by evidence and caselaw. In addition, and in contrast to the Examiner's statements, Applicants respectfully assert that RNAi technology was not a nascent technology as of the earliest effective filing date of the subject application. As Applicants noted in their response to the previous Office Action, Milhavet *et al.* and Agrawal *et al.*, and the other publications previously submitted, have shown significant reduction in endogenous and foreign gene expression in a large variety of cell types, using various RNA species and delivery methods (see, for example, Table 1, at pages 635-636 of Milhavet *et al.*). In addition, inhibition of viral replication has been achieved *in vitro* and *in vivo* using interfering RNA-mediated gene silencing, as demonstrated by Coburn G.A. and Cullen, *J. Virol.*, 2002, 76(18):9225-9231; Lee M-T M. *et al.*, *J. Virol.*, 2003, 77(22):11964-11972; Qing Ge *et al.*, *PNAS*, 100(5):2718-2723; McCaffrey A.P. *et al.*, *Nature*, 2002, 418(6893):38-39; McCaffrey A.P. *et al.*, *Nat. Biotechnol.*, 2003, 21(6):639-644; Hu W.Y. *et al.*, *Curr. Biol.*, 2002, 12(15):1301-1311; and Gitlin L. *et al.*, 2002, 418(6896):430-434, which have been previously submitted.

As Applicants stated above, having the structure and sequence of the target gene (PKC), Applicants submit that one skilled in the art could readily obtain target nucleic acid sequences with the recipient mammal's mRNA. Furthermore, due to the certainty of the genetic code and complementarity, there is a well known correlation between target nucleic acid sequences within a target gene and nucleic acid sequences that interfere with the expression of the target gene. Hence, having the nucleotide sequence of the target gene provides sufficient information to allow one skilled in the art to obtain interfering RNA molecules without resort to undue experimentation. As shown by the Milhavet *et al.*, having the nucleotide sequence of the target gene provides discerning information regarding the sequences of suitable interfering RNA molecules, and leads one of ordinary skill in the art to their selection. As indicated by Milhavet *et al.*,

> All that is needed to implement siRNA-mediated silencing of expression of a gene of interest is the cDNA sequence of that gene, and commercially available reagents with which to perform the synthesis (Milhavet *et al.* page 637, column 1, lines 2-6).

Applicants respectfully submit that, in view of the disclosure of the subject specification as originally filed demonstrating that PKC inhibition would be of benefit in inhibiting RSV infection, and in view of the availability of a broad genus of PKC inhibitors, methods for reducing PKC expression using PKC inhibitors such as interfering RNA are fully enabled. Inhibition of gene expression using nucleic acid inhibitors of various genes (including PKC) has been demonstrated in animal models of other disease states. Accordingly, Applicants respectfully submit that the data and teachings provided within the subject specification is reasonably predictive of inhibition of RSV infection upon inhibition of PKC *in vivo*, and the animal models in the art are sufficiently predictive of PKC gene silencing *in vivo*.

Applicants respectfully maintain that an application for patent is not required to show that a claimed method of treatment of a disease condition results in a cure of that disease condition, or even that clinical efficacy is achieved. The Federal Circuit has made it clear that the showing for therapeutic utility that is sufficient to satisfy the patent laws is not to be confused or equated with the showing required by the Food & Drug Administration for drugs, medical devices, and procedures. See *Scott v. Finney*, 32 USPQ2d 1115 (Fed. Cir. 1994) and Manual of Patent Examining Procedure section 2164.05. Given the state of the art as demonstrated by the evidence presented in the scientific publications previously submitted, and the information provided in the subject specification and the experimental results obtained therewith, one of ordinary skill in the art would reasonably expect that one can target and reduce expression of PKC *in vitro* and *in vivo*, without resort to undue experimentation. Thus, Applicants respectfully submit that the subject specification enables the methods as currently claimed. Accordingly, reconsideration and withdrawal of the rejection under 35 USC §112, first paragraph, is respectfully requested.

In view of the foregoing remarks, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

Doran R. Pace
Patent Attorney
Registration No. 38,261
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: Saliwanchik, Lloyd & Saliwanchik
A Professional Association
P.O. Box 142950
Gainesville, FL 32614-2950

DRP/jil/mv